A COMPARATIVE STUDY OF ORAL VERSUS INTRAVENOUS IRON THERAPY, MATERNAL AND FETAL OUTCOME OF ANEMIA IN PREGNANCY

DISSERTATION SUBMITTED TO

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY, CHENNAI

IN PARTIAL FULFILLMENT OF THE REGULATIONS FOR THE AWARD OF

M.D. DEGREE IN OBSTETRICS & GYNECOLOGY

Guide

Dr. Reena Abraham M.D., DGO

DEPARTMENT OF OBSTETRICS & GYNECOLOGY

P.S.G. INSTITUTE OF MEDICAL SCIENCES AND RESEARCH

PEELAMEDU, COIMBATORE – 641 004

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CERTIFICATE

This to certify that the dissertation entitled **"A Comparative study of oral versus intravenous iron therapy, maternal and fetal outcome of anemia in pregnancy",** is the bonafide work of **Dr. Salini Nair,** in the Department of Obstetrics & Gynecology, PSG Institute of Medical Sciences and Research, Coimbatore, in partial fulfillment of the regulations for the award of M.D. Degree in Obstetrics & Gynecology from the Tamilnadu Dr. M.G.R. Medical University, Chennai.

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Date :

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Place :

LIST OF ABBREVIATIONS

Hb	Hemoglobin
FDA	Food and Drug Administration
RDA	Recommended Daily Allowance
DHA	Docosahexaenoic acid
MCV	Mean Corpuscular Volume
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
CBC	Complete Blood Count
WBC	White Blood Cells
RBC	Red Blood Cells
APH	Antepartum Hemorrhage
PPH	Postpartum Hemorrhage

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INTRODUCTION

Anemia is defined from greek word, without (an) blood (haem) meaning "No blood" Anemia is a global problem. It is a direct cause of 5-25% of maternal deaths and indirect cause in 20-40% of maternal deaths. A recent update of WHO publication on institutional anemia (1992) reports that about half of the pregnant women in the world suffer from constitutional anemia, which is the most common deficiency state.

Iron has for long been considered important for the body, calcined iron (Lauha bhaswa) has been used in ancient Indian medicine. Iron deficiency anemia is the commonest nutritional deficiency in pregnancy, followed by folate deficiency. Deficiency of vitamin B12 is relatively less common in non-industrialized countries.

Incidence of Anemia in Women

Anemia is a problem of gigantic proportions. Some statistics are worth considering

- Anemia, Particularly, Iron deficiency affects 2 billion people world – wide
- Affects 44-56% of pregnant women in developing countries
- Affects 18% of pregnant women in industrialized nations
- Prevalence of anemia in India is about 60% and increases to 80% during pregnancy.
- In India, out of a pregnant population of 22 million women, it affects 13 million pregnant women.
- In India, about 0.5 million women die annually, as a result of pregnancy and its complications, Anemia is the leading contributor to this appallingly high maternal mortality

rate

- Anemia is directly responsible for 20% of maternal deaths and another 20% die due to indirect consequences of anemia like obstetric hemorrhage, sepsis etc.,

The female is always in precarious iron balance during reproductive years in most developing countries.

Most women are not able to develop adequate iron stores during the growth period. Thus women enter pregnancy state with depleted iron stores.

The daily iron requirement of non-pregnant women is 2 mg and in pregnant women is 4 mg per day in first trimester, increases to 6.3mg in second half of pregnancy.

The iron demand during pregnancy is 1000mg. Even after deducing iron conserved by amenorrhea (240-480mg), an additional 500-600mg of iron is required in pregnancy or 4-6mg of absorbed iron, which can only be achieved by mobilizing iron stores in addition to maximum iron absorption from diet. Daily intake of iron should be 40-60mg/day, out of which only 8-10% of iron gets absorbed per day. But the average Indian diet contains only 10-15mg/dl, out of which only 3-5% of iron is absorbed.

Thus, the amount of iron absorbed form the diet, together with that mobilized from stores is usually insufficient to meet the demands imposed by pregnancy, hence the need for supplementation of iron during pregnancy.

Anemia, is defined as reduction in total circulating erythrocyte mass below the critical level which leads to decreased oxygen carrying capacity of blood, which in turn leads to hypoxia.

According to WHO TRS series 405, 1968, it is a condition in which hemoglobin concentration is lower than normal as a result of a deficiency of one or more essential nutrients.

According to WHO TRS series 503, 1972, for the diagnosis of anemia in pregnancy, the hemoglobin concentration should be less than 11gm/dl and a haematocrit of less than 33%.

According to center of disease control in 1990, anemia is defined as hemoglobin less than 11g/dl in the first and third trimester and less then 10.5g/dl in second trimester.

CLASSIFICATION

WHO Classification :

Mild Anemia - 9.1 to 11gm/dl

Moderate Anemia - 7.1 to 9gm/dl

Severe Anemia - < 7 gm/dl

Although hemoglobin of 11gm% is taken as cutoff point as per WHO definition, in developing countries and India, cutoff point is taken as 10.5gm%

According to the guidelines by WHO (1999), hemoglobin percentage is represented in gm/lt, instead of gm/dl.

RECENT CLASSIFICATION

According to WHO 2002

- Mild / moderate anemia – 7.0 to 10.9 gm/dl
- Severe anemia – 7gm/dl

Indian council of medical research

ICMR uses four categories of anemia depending upon hemoglobin levels.

Category 1 - Mild - 10.0 to 10.9g/dl

Category 2 - Moderate - 7.0 to 10.0g/dl

Category 3 - Severe - <7.0g/dl

Category 4 - Very severe - < 4.0g/dl
(Decompensated)

Modern Classification – Kinetic

1. Cytometric :
   a. Normocytic normochromic - Anemia of chronic disease
   b. Microcytic hypochromic - Iron deficiency anemia
   c. Macrocytic normochromic - Vit.B12 deficiency, folate deficiency
2. Erythrokinetic :

   Depends on rates of RBC production and destruction eg. hemolytic anemia, thalassemias

3. Biochemical/molecular classification

   Depends on etiology at molecular level eg. iron deficiency anemia, megaloblastic anemia.

NUTRITION AND WOMEN

The nutritional requirements of women differ in different stages of life. An individual's nutritional health starts to take shape while he/she is in-utero and remains the basic template throughout life. Hence to give the children a well nourished body, a mother must start when she is pregnant. A healthy mother makes a healthy baby who makes a healthy adult and the circle goes on.

Food to be eaten in abundance : Vegetables, fruits, high fibre grains like oats,

wheat bran, bajra, jowar.

Food to be eaten in moderation : Milk and milk products (rich in calcium), breads, some fruits like banana, mango, chikoo, nuts (contain minerals), sea-food.

Foods to be restricted : Red meats (lamb, beef, pork), butter, cheese, ghee, fast food, processed & canned foods

Dietary components – specific dietary components do not appear to have a significant effect on birthweight.

Macronutrients

Calories are the single most important nutritional factor in determining birthweight. Balanced energy/ protein supplements – compared with no supplementation, energy supplementation during pregnancy (300-850 kcal/day with less than 25% of that energy coming from protein) is associated with small increases in maternal weight gain and birthweight, and a greater reduction in the risk of small for gestational age (SGA) infants and stillbirths. Women fed a diet low in cholesterol and saturated fat had a marked decrease in preterm deliveries.

DHA (omega – 3 polyunsaturated fatty acid) appears to be essential for early birth development during gestation and infancy. Some studies have demonstrated better mental growth of offspring of mothers who had taken cod-liver oil. Other studies have reported similar benefits and also improvement in visual acuity and decrease in risk of allergic disorders. Fish oil supplements or fish is recommended to improve neurological, immunological or physical development in the offspring.

Micronutrients

In developing countries, consumption of multivitamins may improve birthweight and

infant mortality.

Calories

Calories are the single most important nutritional factor in determining birth weight. The recommended intake is 340kcal/day in the second trimester and 452kcal/day in the third.

Protein

The fetal/placental unit consumes approximately 1kg of protein during pregnancy, with the majority of this requirement in last 6 months. To fulfill this need the mother should ingest 1.1g/kg/day protein, which is moderately higher than the 0.8g/kg/day recommended for non-pregnant adult women. Animal proteins are considered complete or high quality proteins because they contain all 9 essential amino acids that the body needs for growth and repair of body tissues. Plant based foods are usually incomplete. The deficient amino acids can be obtained from soy products, consumption of foods with complementary amino acids and increased intake of dairy products.

Carbohydrates

The RDA for carbohydrates in pregnancy is 175g/day, up from 130g/day in non-pregnant women.

Calcium

Fetal skeletal development requires about 30 gm of calcium during pregnancy, primarily in the third trimester. This much is easily mobilized from maternal stores. The RDA for calcium is 1000 mg / day in pregnant & lactating women.

Vitamins and Minerals

Women at risk for deficiency include those carrying twins, heavy smokers, strict vegetarians, substance abusers, women with lactose deficiency. Content varies depending on product used. A supplement that contains : Zinc-15mg, Copper -2mg, Calcium-250mg, Vitamin B6-2mg, Vitamin C-50mg, Vitamin D-5mcg (200IU) is useful.

Folic Acid requirements are higher in pregnancy, between 400-600mcg/day, best started in the periconceptional period.

AIM OF THE STUDY

- To assess the efficacy of intravenous iron sucrose when compared to oral iron in the treatment of anemia in pregnancy.
- To compare the overall pregnancy outcome with respect to changes in the
  a. Hemoglobin level
  b. Serum ferritin level
- To conclude that parenteral iron therapy restores iron stores faster and more effectively than oral iron
- To prove that iron sucrose therapy aids in improved fetal outcome with slightly higher increase in fetal weight when compared with oral iron therapy.

REVIEW OF LITERATURE

In a study by Ragip A. Al et al., 2005, established that intravenous iron sucrose is a safe and effective alternative to oral iron in treatment of iron deficiency anemia of pregnancy. It restores blood stores more rapidly and a prompt increase in hemoglobin may be achieved.

In a study by al momen et al, they compared 52 women treated with intravenous iron sucrose with 59 women treated with 300mg of oral iron sulfate and found that intravenous therapy resulted in higher hemoglobin levels in shorter periods compared with the oral therapy group. They concluded that iron sucrose is safe and effective in the treatment of iron deficiency anemia during pregnancy.

In a study by Bayoumeu F et al, an open study involving 50 patients with hemoglobin levels between 8 and 10g/dl and a ferritin value of < 50 mg/dl. The oral group received 240mg of iron sulfate per day for 4 weeks. Treatment efficacy was assessed by measurement of hemoglobin and reticulocytes on days 8,15,21 and 30 and at delivery and of ferritin on day 30 and at delivery. The baby's birth weight and iron stores were noted. They concluded that iron sucrose appears to be a treatment without serious side effects indicated in correction of pregnancy anemia or iron stores depletion.

A study by Yee J et al., this article focuses on iron sucrose, a hematinic, used more widely than any other for more than five decades, chiefly in Europe and now available in North America. Iron sucrose has an average molecular weight of 34 to 60 kd, and after intravenous (IV) administration, it distributes into a volume equal to that of plasma, with a terminal half-life of 5 to 6 hours. Transferrin and ferritin levels can be measured reliably 48 hours after IV administration of this agent. Iron sucrose carries no "black-box" warning, and a test dose is not required before it is administered. Doses of 100mg can be administered over several minutes, and larger doses upto 300mg can be administered within 60 minutes. Iron sucrose has been associated with a markedly lower incidence of life-threatening anaphylactic reactions and may be administered safely to those with previously documented intolerance to iron dextran or iron gluconate. Nonanaphylactic reactions, including non-life threatening hypotension, nausea and exanthema, also are extremely uncommon with iron sucrose.

In a study by G. Perewusnyk et al, they assessed that iron-deficiency anemia forms the commonest nutritional pathology in pregnant women. The current gold standard to detect iron deficiency remains the serum ferritin value. Previously there was general consensus against parenteral iron administration i.e. parenteral iron was only recommended for special conditions such as unresponsiveness to oral iron, intolerance to oral iron, severe anemia, lack of time for therapy etc. However, especially in hospital settings, clinicians regularly face these conditions but are still worried about reactions that were described using iron preparations such as iron-dextrans. A widely used and safe alternative is the iron-sucrose complex, numerous reports show the effectiveness and safety of the iron-sucrose complex. Good tolerance to this iron formulation is partly due to the low allergenic effect of the sucrose complex, partly due to slow release of elementary iron from the complex. By using parenteral iron-sucrose in cases of

severe iron deficiency, anemia during pregnancy is treated efficiently and safely according to the results, and rate of blood transfusion could be reduced considerably to below 1% of patients per year.

In a study by Suheyl Asma et al, this study aimed to evaluate the therapeutic effectiveness, safety, and cost of intravenous iron sucrose therapy. The computerized database and medical records of 453 patients diagnosed with iron deficiency anemia, who received intravenous iron sucrose therapy for iron deficiency anemia between 2004 and 2008 were reviewed. The improvement of hematologic parameters and cost of therapy were evaluated 4 weeks after therapy. All patients responded to intravenous iron therapy, the therapy was well-tolerated. Although the cost of intravenous iron sucrose therapy may seem high, a lack of adherence to therapy and side effects including gastrointestinal irritation during oral iron therapy were not experienced during intravenous therapy.

In a study by Hallak M et al, the objective of this study was to determine the safety and efficacy of maternal intravenous iron administration to avoid blood transfusion in patients. Patients with persistent iron-deficiency anemia complicating pregnancy were included in this study. The total iron amount needed to regenerate iron stores was calculated according to hemoglobin and the patients weight.

Hemoglobin, hematocrit, mean corpuscular volume, serum iron, transferring, and ferritin were evaluated at the start and conclusion of therapy as well as two weeks afterward. Twenty – six patients were included in the study, four of them delivered during the therapy course. The hemoglobin increased at the start and end of therapy, respectively and continued to rise two weeks later. All values increased over 2 weeks except for transferrin value, which was decreased. Only mild and transient side effects were occasionally reported. They concluded

that intravenous iron administration during pregnancy is an effective method of regenerating hemoglobin and iron stores. It should be considered for patients with severe iron-deficiency anemia complicating pregnancy.

A study by Milman N, focuses on the occurrence, prevention and treatment of anemia during pregnancy. Iron deficiency anemia is the most prevalent deficiency disorder and the most frequent from of anemia in pregnant women. The diagnosis relies on hemoglobin, a full blood count and plasma ferritin. Among fertile, non-pregnant women, approximately 40% have ferritin of less than or equal to 30ug/l, i.e. small or absent iron reserves and therefore an unfavourable iron status with respect to upcoming pregnancy. Requirements for absorbed iron increase during pregnancy from 0.8mg/day in the first trimester to 7.5mg/day in the third trimester, on the average approximately 4.4mg/day and dietary measures are inadequate to reduce the frequency of iron deficiency anemia. Treatment with intravenous iron is superior to oral iron with respect to the hematological response. Intravenous iron of 600-1200mg should be considered as first option in profound iron deficiency anemia i.e. hemoglobin of <90g/l in any trimester beyond 14 weeks gestation. This study concluded that profound iron deficiency anemia has serious consequences for both woman and fetus and requires prompt intervention with intravenous iron.

In a study by Breymann C, it states that inadequate understanding of the complex chemistry of parenteral iron administration was previously responsible for serious side effects, such as toxic and allergic reactions and even anaphylactic shock, in particular with dextran preparation. However, the current type II iron complexes that release iron to the endogenous iron – binding proteins with a half-life of about 6 hours are not only effective but carry a minimal risk of allergic accident and overload. They concluded that the departmental data

collected over 8 years and backed by experience in 25 countries indicate that iron sucrose complex therapy is a valid first-line option for the safe and rapid reversal of iron-deficiency anemia of pregnancy.

In the Cochrane review by Cuervo LG, they identified 17 randomized controlled trials comparing treatments for iron-deficiency anemia in pregnancy, involving 2578 women. They came to the conclusion that daily oral iron treatment improves hematological indices but causes frequent gastrointestinal adverse effects. Parenteral iron, on the other hand, enhances hematological response, compared with oral iron but there are concerns about possible adverse effects.

In the study by Silverstein SB, states that although oral iron is appropriate for most iron-deficiency anemia patients, many patients do not respond to or may be intolerant of oral iron, or may experience bleeding of sufficient magnitude to require higher iron doses than that achievable with oral iron. Intravenous iron therapy is a useful option for these patients. Intravenous iron sucrose and ferric gluconate have superior safety profiles compared to high-molecular weight iron dextran. The food and drug admiistration's (FDA) approval of erythropoietic – stimulating agents to treat certain types of anemia has increased usage of intravenous iron for functional iron deficiency anemia.

IRON METABOLISM

Distribution :

Normal distribution includes :

1. Hemoglobin iron
2. Storage iron

3. Myoglobin iron
4. Labile pool iron
5. Transport iron

The dispersion of iron in each compartment can be affected by concurrent disease processes as well as by nutritional status.

1. Hemoglobin iron :

Constitutes over 60% of total body iron. During pregnancy, it is increased by 20%, in association with the concomitant increase in total blood volume, hemoglobin molecule contains 0.34% iron by weight.

2. Storage iron :

Accounts for 30% of total body iron. This iron compartment is equally divided into

- Hemosiderin : found only in the cells of the reticuloendothelial system and contains approximately 25% of iron by weight.
- Ferritin : found in plasma and virtually all cells of body contains 30% of iron by weight

Ferritin has the ability to release and attach iron rapidly and therefore plays a direct role in iron absorption.

3. Myoglobin iron :

3% distribution is myoglobin iron

4. Labile iron pool :

A study of kinetics has identified the iron that moves from the plasma to interstitial and intracellular fluid as labile iron pool, constitutes 10% of iron storage. Contains 80mg of iron.

5. Parenchymal iron :

Represents 0.2 – 0.5% of body's storage iron, contains approximately 6mg iron by weight.

6. Transport iron :

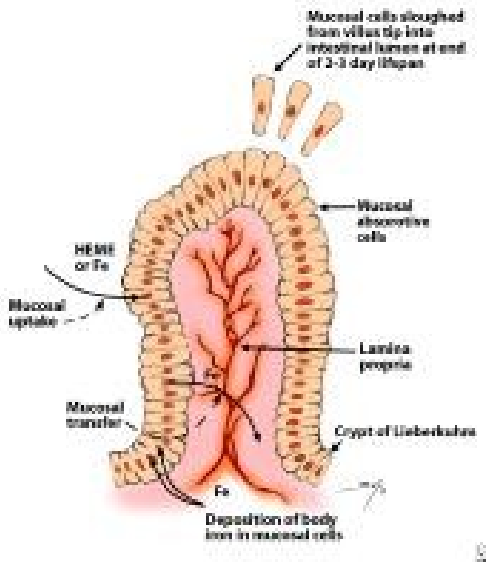
Smallest compartment of iron storage about less than 0.1%. It is the most active compartment.

ABSORPTION

Absorption occurs in upper part of small intestine (duodenum and jejunum). The average daily diet contains 10-20mg of iron.

Dietary iron is present either as,

- Heme is better absorbed (upto 35%) but forms a smaller fraction of dietary iron.
- Inorganic iron (nonheme iron, 5%) is mostly in ferric form, needs to be reduced to ferrous form before absorption can take place.



The iron is absorbed mainly in ferrous form (Fe^{++}) from elemental iron rather than the ferric form (Fe^{+++})

Mucosal cells in the proximal small intestine mediate iron absorption. Intestinal cells are born in the crypts of lieberkuhn and migrate to the tips of the villi. The cells are sloughed

into the intestinal lumen at the end of their 2-3 day lifespan. Absorptive cells remain attuned to the body requirements for iron by incorporating proportionate quantities of body iron into the absorptive cells. This iron and recently absorbed iron decrease uptake of iron from the gut lumen by satiation of iron-binding proteins with iron, by stimulating an iron-regulatory element, or both. The incorporation of iron into these cells in quantities proportional to body stores of iron also provides a limited method of increasing iron excretion in individuals replete in iron.

Dietary Pathway :

Three pathways exist in enterocytes for update of food iron. Most absorbed iron is derived from heme. Heme is digested enzymatically free of globin and enters the enterocyte as a metalloporphyrin. Within the cell, iron is released from heme by heme oxygenase to pass into the body as inorganic iron. Most dietary inorganic iron is ferric iron. This can enter the absorptive cell via the integrin –mobilferrin pathway (IMP).

Some dietary iron is reduced in the gut lumen and enters the absorptive cell via the DCT-1 (divalent cation transporter) pathway. The proteins of both pathways interact within the enterocyte with paraferritin, a large protein complex capable of ferrireduction. Excess iron is stored as ferritin to protect the cell from oxidative damage. Iron leaves the cell to enter plasma, facilitated by ferroportin and hephaestin, which associate with an apotransferrin receptor. The enterocyte is informed of body requirements for iron by transporting iron from plasma into the cell using a holotransferrin receptor.

RECENT CONCEPTS:

The regulation of iron absorption by the intestine has crucial implications for the body, because humans have no physiological pathway for the excretion of iron, making control at entry as must.

The cells of the duodenal mucosa can sense the requirements of iron by the body as a whole and automatically get programmed by the sensor mechanisms as they mature into absorptive enterocytes.

According to recent research findings in this vital area, the enterocytes lining the

absorptive villi close to gastroduodenal junction are responsible for all iron absorption.

The acidic PH of the gastric effluent helps dissolve ingested iron and provides a proton-rich milieu.

This facilitates reduction of ferric iron to its ferrous form by an enzyme known as ferric reductase, located at the apical brush border of the enterocyte.

The ferrius form then enters the enterocyte with the help of a transporter protein known as DMT 1 (divalent metal transporter 1) which is also situated at the apical brush border.

Incidentally DMT 1 plays an important role in the transport of many divalent ions such as manganese, cobalt, copper, zinc, calcium etc.

Once inside the enterocyte, iron is stored as ferritin if it is not immediately needed by the body and this storage form will be eliminated in the faeces when the cell is shed eventually.

STORAGE OF IRON :

Iron is stored in liner, spleen and bore narrow. The storage form is ferritin.

EXCERTION OF IRON :

The total amount of daily iron loss average 0.16% epidermal cell loss and sweat amount to a daily loss of 0.2mg, while iron loss in urine averages 0.1mg/day. Menstruating women usually lose 25 to 45 ml of blood with each period, which is a loss of 13 to 23mg of iron.

THREE INDEPENDENT CONTROLS :

The control process has three dimensions, which are independent of each other but may

overlap from time to time.

First :

It is influenced by recent dietary iron intake.

This is called “Dietary regulator”.

With this in operation, absorptive cells are resistant to iron intake for several days after large dietary bolus of iron. This was called “Mucosal block” by scientists an earlier era.

Second :

Iron absorption can be modulated considerably in response to body iron stores.

This is called “stores regulator”

In other words, this regulator senses total body stores, and not dietary intake.

Third :

An unidentified signal communicates the state of bone narrow erythropoiesis to the intestine.

This is called “erythroid regulator”.

The exact mechanism of this regulator is not known, but it is believed to be carried from the bone narrow to the intestinal cells.

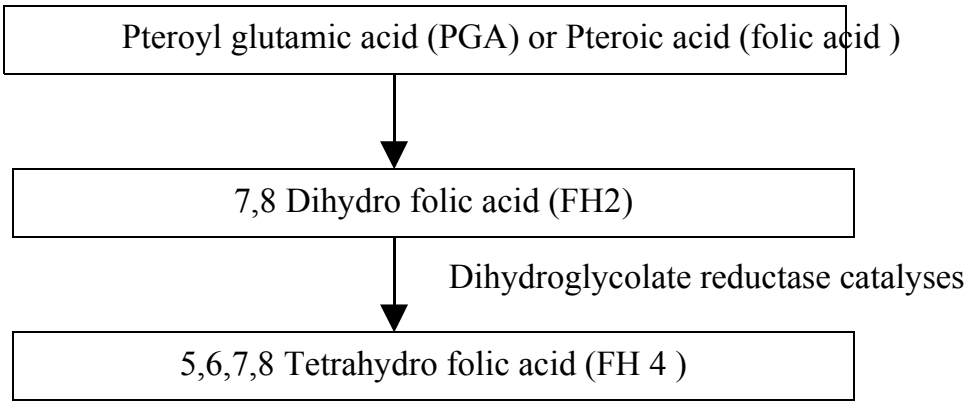
FOLIC ACID

The term folic acid is derived from its widespread presence in green leafy vegetables (Folium – leaf)

Sources : The richest sources of folate are green leafy vegetables and fruits.

Spinach, lettuce, asparagus, broccoli and lima beans are excellent sources of folate, while the best fruit sources are lemons, melons and bananas. Folic acid is absorbed primarily in proximal jejunum and must be provided in the diet. Before folic acid can be absorbed, it must be

reduced to its monoglutamate form (FH1). Pancreatic conjugates within the intestine are responsible for this metabolic process. Once this process is complete, FH1 enters the mucosal cells.



Appropriate DNA synthesis and amino acid production requires formyl FH4 derivatives. Insufficient levels of folic acid will preclude appropriate DNA synthesis and subsequently lead to the manifestations noted in megaloblastic anemia.

NORMAL HAEMATOLOGIC EVENTS ASSOCIATED WITH PREGNANCY

The "Plethora of pregnancy" has been recognized clinically for many centuries.

The "Plethora" results from an expanded blood volume in pregnancy

This pregnancy induced hypervolemia has several important functions :

1. To meet the demands of the enlarged uterus with its greatly hypertrophied vascular system.
2. To protect the mother, and in turn the fetus, against deleterious effects of impaired venous return in the supine and erect positions.
3. To safe guard the mother against the adverse effects of blood loss associated with parturition.

The increase in blood volume associated with pregnancy totals between 1lt to 2lt, depending on the size of the patient and several other variables that may enhance or cancel one another. The two variables that have the greatest effect on blood volume changes are the independent variation of the plasma volume and the red cell volume.

These are not at all synchronous, and their discordance accounts for most of the apparent "anemia" associated with pregnancy.

- Plasma volume : increases first, beginning half way through 1^{st} trimester, and reaches a peak about the 28^{th} to 30^{th} week, from then on, it slowly rises until term, but the rate of rise is so slow that it simulates a plateau effect. The total plasma volume expansion ranges from 25 to 50%, the wide range resulting from individual variation among normal pregnancies.
- The red cell volume, begins to rise in pregnancy late in the first trimester and continues to rise throughout pregnancy, following a different curve from that of the plasma volume. The total increase in red cell mass during pregnancy approximates 20 to 40%.

For the individual woman, the expansion of red cell mass is less than the proportional expansion of plasma volume.

Because the increase in red cell mass in pregnancy lags behind and is of smaller magnitude than the expansion of plasma volume, pregnancy demonstrates " an anemia of dilution."

At approximately the 30th week of pregnancy, plasma volume expansion plateau and the progressive decline of hemoglobin concentration stops.

During the last trimester a slight rise in the hemoglobin concentration towards the prepregnant level may occur.

With delivery, there is a loss of some of expanded blood volume associated with pregnancy, averaging, 500ml for a normal vaginal delivery and larger amounts if delivery is by cesarean section.

This expected and normal loss associated with delivery leaves the newly delivered woman still relatively hypervolemic, which accounts for the tolerance for hemorrhage characteristic of pregnant patients.

During the puerperium, there is rapid restoration to prepregnant blood, plasma and red cell volume levels, which takes place as rapidly as within one week.

The most interesting of these events of volume contraction is the fate of expanded red cell mass, with its precious iron content.

TABLE - I

Physiological changes in blood indices during pregnancy

Chacteristics	**Normal Adult women**	**32-34 weeks Gestation**	**Increased / Decreased**
Plasma volume (ML)	2600	3850	1250 increased

Red Cell Mass (ML)	1400	1640 (without iron supplementation)	
Hemoglobin (g/dl)	12-14	11-12 (without iron supplementation)	Decreased
Red Bl			Decreased
Packed cell volume	0.36-0.44	0.32-0.36	Decreased
Mean corpuscular volume (f1)	80-97	70-95	Decreased
Mean corpuscular hemoglobin (pg)	27-33	26-31	Decreased
Mean corpuscular hemoglobin concentra	32-36		
Serum Iro			Decreased
Total iron			Increased
Percentag			Decreased
Requirements of iron (mg/day)	1.5-2.0	4.0	Increased

Increased requirement of Iron during pregnancy

↓

Increased absorption from intestine

↓

Mobilization of Iron stores

↓

If inadequate intake, reduced absorption or chronic bleeding

↓

Iron Stores are depleted → stage I

[↓ serum ferritin]

↓

Serum ferritin levels fall, and transferrin saturation decreases

↓

Fig - 1

PATHOPHYSIOLOGY AND STAGES OF IRON – DEFICIENCY ANEMIA :

↓

Decreased supply of iron to erythroid precursor

↓

Iron – restricted erythropolesis → Stage II

[↑ Free erythrocyte protoporphyrin]

↓

Accumulation of free erythrocyte protoporphyrin

↓

Reduced erythrocyte indices → stage III

[↓ Hemoglobin

↓ MCV, MCH, MCHC]

↓

CAUSES OF IRON – DEFICIENCY ANEMIA

- Increased requirements
- Low intake and /or bioavailability of dietary iron

Average cereal and legume - based diet, as consumed in most developing countries has 20 – 22 mg of iron which is adequate for an adult. Absorption of 10% would be needed to maintain iron balance. But the bioavailability of iron from such diet is very poor (3-5%) due to presence of phytates, tannins, oxalates, polyphenots, calcium salts and deficiency of vitamin C.

- Infections and infestations

They contribute to iron deficiency anemia by promoting iron loss.

1. Chronic malaria : P. Falciparum malaria is the chief cause of severe anemia amongst

endemic areas of tropical Africa. It leads to anemia by causing chronic hemolysis, erythropoiesis suppression and secondary folate deficiency.

2. HIV infection : Upto 70% of patients who have AIDS are anemic. Aetiology is multifactorial.
3. Helminthic infestations : Attempts to control these infestations are critical for anemia prevention in areas of endemicity.

- ✓ Hookworm : N. americanus and A. duodenale causes blood loss from small gut mucosa, the loss being proportional to number of worms. A moderate hook worm load can induce a fecal iron loss of 3.4 mg/day.
- ✓ Schistosomiasis : S.hematobium causes urinary losses by damaging urinary tract. Mean iron loss in cases of heavy infestation can be 0.7mg/day. The infection is limited to Africa and middle east.
- ✓ Round worm and trichuriasis : Causes gastric and intestinal ulceration and provokes blood loss, though of a less severe degree than that observed in the above infestations.

EFFECT OF ANEMIA ON PREGNANCY

Maternal effects :

Mild anemia : May not have any effect on pregnancy and labour excepting that she will have low iron stores if she ventures into second pregnancy and may become moderately to severely anemic.

Moderate anemia : May cause increased weakness, lack of energy, fatigability and poor work performance.

Severe anemia : On the other hand is associated with poor outcome.

During Pregnancy :

1. Pregnant woman after four months of pregnancy starts looking pale and is not able to cope with her activities. This is because, by fourth month, iron requirement of the fetus starts and fetal blood is formed.
2. High susceptibility to urinary tract infection, genital tract infection and frequent colds and cough.
3. Swollen feet and /or generalized swelling
4. Breathlessness, development of a 'hemic murmur' in the heart
5. Preterm labour
6. Eventually cardiac failure.

During labour, the woman is at greater risk

1. For APH and PPH. Even normal amount of blood loss may lead to collapse and death.
2. Fetal anoxia and distress. May even end up in still-birth.

Postpartum complications:

1. Failure of lactation
2. Puerperal sepsis
3. Subinvolution
4. In case, operative procedures are carried out, delayed wound healing.

Twenty percent of all maternal mortality is due to anemia.

The effects of anemia on the fetus are also significant:

1. Low birth weight babies
2. Birth asphyxia

3. Chronic neonatal illness “Inability to thrive”
4. Poor iron stores lead to development of anemia at age 10 months.
5. Increased perinatal infant mortality rates.

DIAGNOSIS OF IRON DEFICIENCY ANEMIA

- Hemoglobin estimation : is the most practical method of diagnosis as it is cost – effective and can be easily performed by a trained technician. The taliquists method of HB estimation is easy and simple to do but is not very accurate. The copper – sulphate method also has many drawbacks and is not reliable. Sahli’s method is reliable and accurate when done by experts and is the most commonly used method, although cyanometh – hemoglobin method appears to be most accurate.
- Peripheral blood film : is another bedside indicator for diagnosis of anemia which will also differentiate between iron deficiency anemia, folate deficiency anemia and hemolytic anemia. In iron deficiency anemia, there is microcytosis (small red cells), hypochromia (pale red cells), anisocytosis (varying size of cells) and poikilocytosis (abnormal shapes of cells)
- CBC count : This documents the severity of the anemia. In chronic iron deficiency anemia, the cellular indices show a microcytic and hypochromic erythopoiesis, i.e. the MCV, MCH, and MCHC have values below the normal range in iron deficiency anemia. Normal values are 75-1400 cubic microns, 24-33 micro microns and 30-36% respectively of the three indices and values less than lower limits, is indicative of iron deficiency anemia.

  Often the platelet count is elevated (>450.000/ul), this normalizes following iron therapy.

The WBC count is usually within reference ranges (4500-11.000/ul)

- Other blood indices : are serum iron (normal 60-175ugm/dl), total iron binding capacity (TIBC, normal <300mg%) free red cell protoporphyrin. In iron deficiency anemia, serum iron is less than 60ugm/dl and TIBC is >300mg%.
- Serum ferritin estimation : gives better picture of stored iron, as is bone marrow examination for iron. Ferritin is the major storage compound of iron and serum ferritin reflects this stored iron. Serum ferritin falls during second and third trimester and is falsely increased in chronic infections, liver diseases and some neoplasms. Iron deficiency is suspected, if ferritin is less than 35ugm/l and less than 12ugm/l it is diagnostic of depleted iron store. A normal serum ferritin can be seen in patients who are deficient in iron and have coexistent diseases (hepatitis, anemia of chronic disorders).
- Transferrin receptor concentration : This is the best indicator till date, but unfortunately not yet routinely available in most hospitals in India. Levels of serum transferrin receptor (TFR) are increased in iron deficiency anemia.
- Bone marrow examination : by stained marrow preparation to see iron stores is most accurate, but not practical in all cases as it is invasive. The absence of stainable iron in a bone marrow aspirate that contains spicules and a simultaneous control specimen containing stainable iron permits establishment of a diagnosis of iron deficiency without other laboratory tests.

Bone marrow examination is done only in cases where there is no response to iron therapy after 4 weeks or when Kalazar is suspected or in suspected hypoplastic or aplastic anemia.

MANAGEMENT

Parenteral iron therapy :

Parenteral iron is practical, safe, easy and effective way to administer iron, Parenteral iron restores iron stores faster and more effectively than oral iron. In India and other developing countries, there is need to supplement iron to every pregnant woman because iron deficiency exists in most pregnant women. If all pregnant woman receive parenteral iron along with folate therapy, it should be possible to prevent iron-deficiency anemia in pregnant women. This also improves overall pregnancy outcome.

Different types of parenteral iron :

Iron sucrose

Iron dextran

Iron gluconate

Iron sucrose : It is dissociated by the reticuloendothelial system into iron and sucrose. The iron is transferred from the blood into iron stores that are located in the liver and bone marrow. The iron binds with ferritin and then is available for use by the body. It is more readily available for erythropoiesis than iron dextran. It is assigned to pregnancy category B by the

FDA, it is an FDA – approved drug.

Iron gluconate : It is a stable macromolecular complex. The iron is more readily available for use because the complex does not have to be degraded.

Iron dextran : It is absorbed after injection into the capillaries and the lymph system. It is associated with adverse side effects, hence it is not the preferred drug of choice.

Iron Sucrose

Advantages	Disadvantages
Does not require a test dose	Side effects include hypotension, pruritus, cramps, nausea, vomiting and headache.
Less gastrointestinal symptoms	Costly
No risk of anaphylaxis	
Good Bioavailability	

Different types of oral iron supplements :

Types	Molecular iron	Elemental iron
Ferrous sulphate	200 mg	60 mg
Ferrous gluconate	320 mg	36 mg
Ferrous fumarate	200 mg	67 mg
Ferrous calcium citrate	556 mg	50 mg
Ferrous succinate	100 mg	35 mg

Disadvantages of oral iron therapy :

1. Intolerance
2. Unpredictable absorption : there are many factors which can inhibit iron absorption and utilization like antacids, oxalates and phosphates
3. Replenishing the iron stores is difficult
4. Poor compliance

Ferrous sulphate ($FeSO_4$)

Advantages	Disadvantages
Free government supply	20% Intolerance
Dissolves quickly	GI disturbances – diarrhea, nausea, constipation
	Oxidative damage to mucosa
	- Passive absorption - Iron intoxication

Iron Sucrose :

It is dissociated by the reticuloendothelial system into iron and sucrose. The iron is transferred from the blood into iron stores that are located in the liver and bone marrow. The iron binds with ferritin and then is available for use by the body.

Conditions where iron sucrose therapy is unsuitable :

1. In patients with known hypersensitivity to iron sucrose or any of its inactive components.
2. In patients with evidence of iron overload
3. In patients with anemia due to other causes, and not due to iron-deficiency.

MATERIALS AND METHODS

A Comparative study of changes in hemoglobin, maternal and fetal outcome, with oral

and intravenous iron preparation in pregnant women with anemia complicating pregnancy. This study was undertaken in the department of obstetrics & gynecology at PSG Institute of Medical Sciences & Research during the period October 2008 – October 2009.

This study was conducted to prove that iron sucrose is well – tolerated and effective in pregnant women, with anemia complicating pregnancy.

A total of 100 pregnant women were randomly selected, who fulfilled the inclusion and exclusion criteria.

Inclusion criteria :

- Primigravida and multigravida between 24 and 36 weeks of gestation.
- Pregnant women with a hemoglobin level between 6 and 9gm%
- Women with established iron deficiency anemia
- Women with no prior history of blood transfusions
- Women who are not on any therapeutic iron therapy.

Exclusion criteria :

- History of hematological disease
- Multiple pregnancy
- Intolerance to iron derivatives
- Recent administration of iron therapy
- Women with risk of pre-term labour
- Women with medical complications

These 100 pregnant women, between gestational age 24 and 36 weeks were divided into two groups :

Group A : Consisted of pregnant women, who were given oral iron, a total of 300 mg of elemental iron per day, three 100mg iron tablets per day was administered.

Group B : Consisted of pregnant women who were given iron sucrose at the rate of 200mg every other day, the dose for total iron sucrose was calculated from the following formula :

weight x (target hemoglobin – actual hemoglobin) x 2.4 + 500 mg (iron stores)

In the formula, weight represented the patient's weight before pregnancy in kilograms, target hemoglobin was set at 11g/dl.

In each infusion, the maximum total dose administered was 200mg iron sucrose in 100ml of normal saline, slow IV infused over 30 minutes. Monitoring was done throughout the infusion to observe for any side effects.

Indicators of response to iron sucrose therapy :

1. Improved look of the patient
2. Better appetite
3. General feeling of well – being
4. Hematological improvement :-
    a. Rise in hemoglobin values
    b. Increase in serum ferritin levels

If there is no significant improvement evident clinically and hematologically within three weeks, then diagnostic re-evaluation is needed.

Procedure of Study :

On entry into the study, eligibility was checked according to the inclusion and exclusion criteria and informed consent was taken from each patient.

Visit I :

Information, regarding patient's name, address, age, and history of amenorrhoea was obtained and results of general and obstetric examination were noted, maternal weight was noted.

Investigations included estimation of hemoglobin value, serum ferritin level and peripheral smear examination to note the type of anemia.

Iron tablets along with folic acid were given to the oral iron group.

They were advised regarding diet and were asked to take the iron tablet between meals, and not take coffee or tea before and after taking tablets. They were explained about repeating investigations during follow-up visits, after 3 weeks and 8 weeks respectively.

The iron sucrose group was also administered folic acid along with therapy and were advised to avoid oral iron during iron sucrose therapy and thereafter. They were advised to report any adverse side effects immediately.

They were explained about repeating investigations during follow-up visits, after a period of 3 weeks and 8 weeks respectively.

Visit II :

After a period of 3 weeks, the pregnant women were examined clinically and maternal

weight was noted. Hemoglobin and serum ferritin estimation was done in both groups to note the improvement in values.

The side effects volunteered by the women were noted and they were advised to continue tablets, in the oral iron group. The iron sucrose group were advised to continue folic acid, and to avoid oral iron.

On subsequent visits, general and obstetric examination was done and maternal weight and adverse side effects were noted.

Visit III :

After a period of 8 weeks, hemoglobin and serum ferritin estimation was done to note the improvement in values. Any adverse side effects was noted.

After delivery birth weight of the baby was noted, and the oral iron group was advised to continue iron tablets for the next 3 months post – partum.

Hemoglobin estimation was done by sahli's method, which is most practical, cost – effective and commonly used method.

Principle :

Hemoglobin is converted to acid hematin by the addition of N/10 or 0.1 N hydrochloric acid and the resulting brown colour is compared with standard brown glass reference blocks.

The intensity of the brown colour depends on the amount of acid hematin, which in turn, depends on the amount of hemoglobin in the blood sample.

The sahli's hemoglobinometer consists of a

- Standard brown glass mounted on a comparator and a graduated tube.
- A special pipette to measure out 20 cumm of blood, this pipette is supplied with the

instrument.

- The tubes commonly used now are square with graduations in percent on one side and grams per 100ml on the other side.

Procedure :

N/10 HCL was placed in the tube upto lower meniscus, blood was drawn upto 20mm mark in the pipette and transferred to the acid in the tube. The pipette was rinsed well by drawing up some of the acid and blood and by shaking the tube well and wait for 10 minutes to allow the brown colour to develop i.e. for formation of acid hematin. Then the solution was diluted with distilled water, adding a few drops at a time with continuous stirring, until the colour matched with the glass plates in the comparator.

The matching was done against natural light. The level of the fluid was noted at its lower meniscus and reading corresponding to this level on the scale was read in gms/100ml.

SAHLI'S HEMOGLOBINOMETER

Peripheral smear was done to know the type of anemia.

Procedure :

A small drop of capillary blood was placed about 1 or 2 cm from one end of a pre-cleaned slide.

Immediately, another slide with a smooth edge was placed at an angle of 25 degrees and moved backwards to make contact with the drop.

The drop of blood should spread out quickly along the line of contact of the spreader with the slide. The blood film was then spread by a rapid, smooth, forward movement of the spreader until all the blood has spread or the edge of the slide is reached. The ideal thickness of the smear was such that there was some overlap of red cells throughout majority of the length of the smear with separation and no distortion towards the tail of the film. The air-dried blood smear was fixed by covering the film with acetone-free methyl alcohol for 1 minute.

Denaturation of proteins is required to prevent hemolysis of the RBCs. The slide was flooded with Leishman's stain for 5 minutes.

Double the volume of distilled water was added and left for 10 minutes. The slide was washed with distilled water. The slide was air-dried and the back of the slide was wiped clean and was observed under the microscope, and the type of the anemia was noted.

Serum ferritin is done to know the iron stores. This method is done by the Electrochem

Illuminescence Immunoassay.

Procedure :

10 ul of sample and a monoclonal ferritin – specific antibody form a complex. After addition of streptavidin – coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin.

The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.

Results are determined via a calibration curve which is instrument – specifically generated by 2-point calibration and a master curve provided via the reagent bar code.

The following parameters were noted :

1. Hemoglobin levels and serum ferritin values :

Visit I – Baseline

Visit II – After 3 weeks

Visit III – After 8 weeks

2. Adverse reaction monitoring

No direct leading questions were asked to elicit side effects. Only those side effects volunteered by the pregnant women, were recorded.

They were asked to report immediately if there were any unpleasant symptoms during iron sucrose therapy or oral iron therapy.

This report included a detailed description of the symptoms, time of onset and duration, whether treatment was discontinued and corrective measures taken.

3. The birth weight of the baby at delivery was recorded.

OBSERVATIONS

In the present study, women who were asked to take oral iron preparation containing 300mg of elemental iron were allocated to group A.

Women who were asked to take iron sucrose therapy were allocated to group B.

TABLE – II

DEMOGRAPHICAL DATA

Particulars	Group A (Oral Iron)	Group B (Iron Sucrose)
No. of patients	50	50
Mean age (yrs) ±SD Range	22.7 ±2.4 18-29	21.4 ± 2.1 18 -28
Mean gestational age	26.7 ± 4.0	27.7 ±3.3
Mean wt (kg) range	52.75 ±8.27 40-75	54.14 ±7.21 40 – 70
No. Discontinued	None	None

In this study,

In group A – age of cases were ranging from 18 – 29 years with mean age of 22.7 ± 2.4 years and mean weight was 52.75 ±8.27 kg.

And in group B – age of cases were ranging from 18-28 years with mean age of 21.4 ± 2.1 years and mean weight was 54.14 ±7.21kg.

This was found to be statistically insignificant.

No Patients from both the groups discontinued the study.

TABLE – III

Mean Hemoglobin Percentage

Mean Hb%	VISIT – I (Baseline)	VISIT – II (After 3 weeks)	VISIT – III (After 8 weeks)
Group A (Oral Iron)	8.22	9.15	9.93
Group B	8.12	10.35	11.57

(Iron Sucrose)			

This table shows the mean hemoglobin concentration at the first visit i.e. baseline hemoglobin and the rise in hemoglobin values in the subsequent visits.

Fig.2 : Mean hemoglobin values in patients treated with Oral iron & Iron sucrose

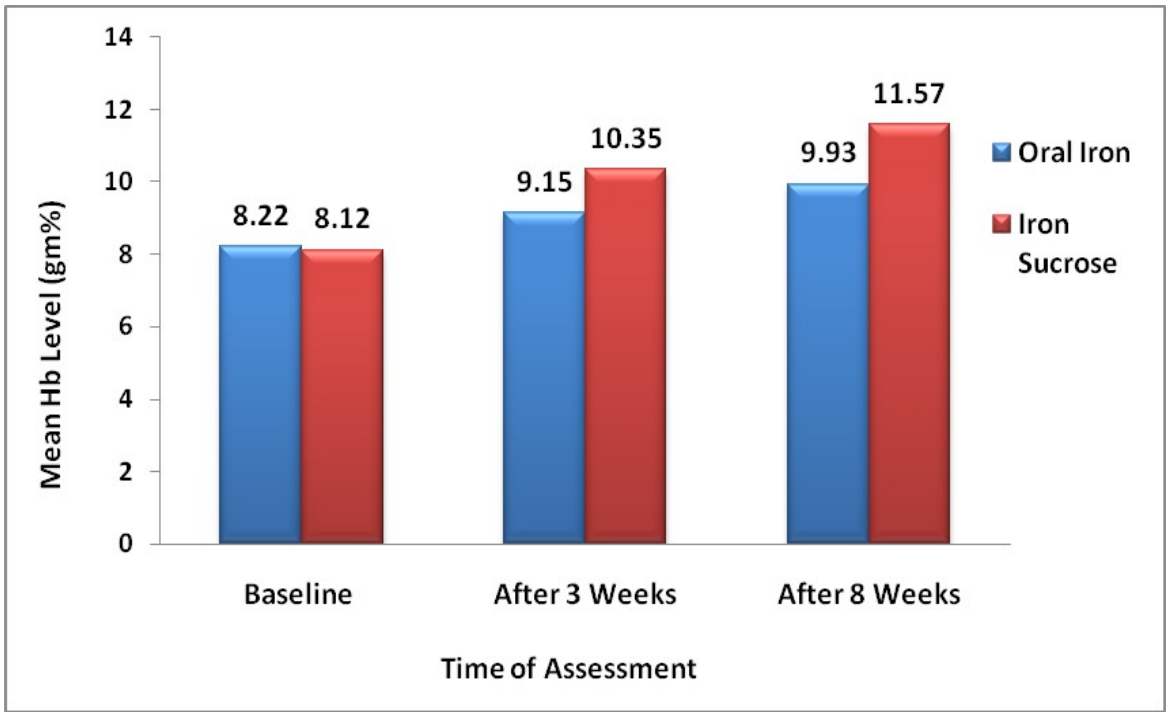
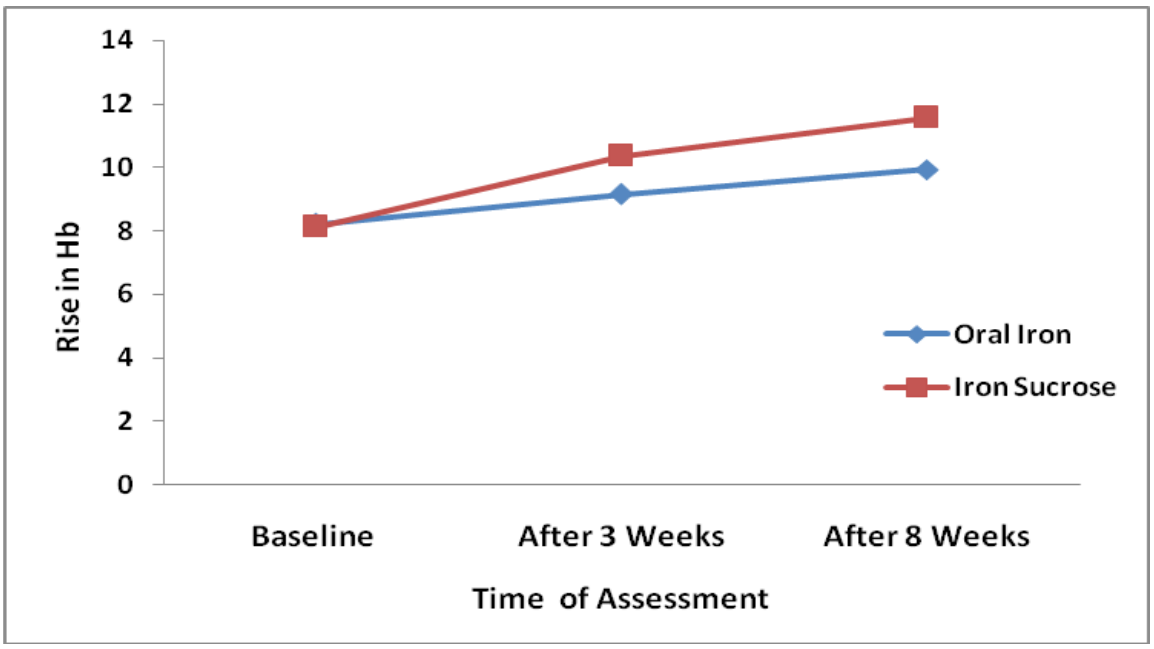


Fig -3 Change in Hemoglobin Level



The comparative changes in mean hemoglobin percentage between group A & group B shows a significant improvement in the iron sucrose group, with a t-value of 12.45 and $p < 0.001$, which was statistically significant

TABLE – IV

Mean Serum Ferritin Percentage

Mean sr. ferritin	VISIT – I	VISIT – II	VISIT – III

	(Baseline)	(After 3 weeks)	(After 8 weeks)
Group A (Oral Iron)	7.82	17.4	26.64
Group B (Iron Sucrose)	6.86	30.62	70.64

This table shows the mean serum ferritin value at the first visit (baseline) and the rise in the serum ferritin levels in the subsequent visits, after 3 weeks and again after 8 weeks.

Fig. 4 : Mean Serum Ferritin levels

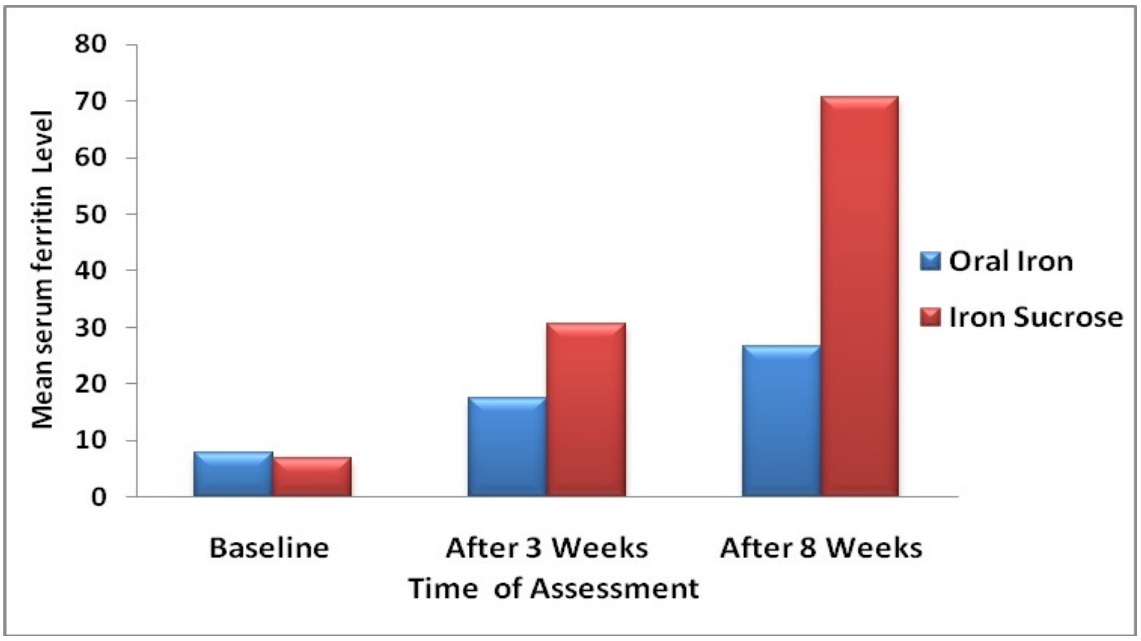
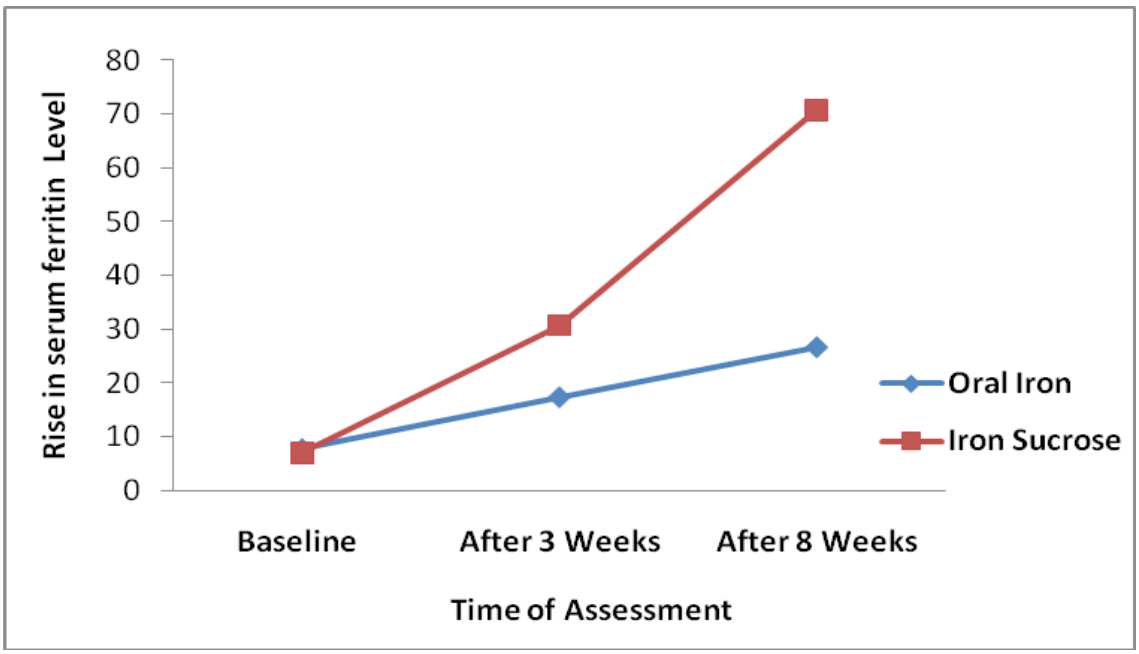


Fig. 5 : Change in Serum Ferritin level



The comparative changes in the mean serum ferritin values between group A and group B shows a significant improvement in the iron sucrose group, with a t-value of 11.39 and $p<0.001$, which was statistically significant.

TABLE – V

Side Effects

Side effects	Group A (Oral Iron)	Group B (Iron Sucrose)

Nausea	2	-
Heartburn	1	-
Abdominal discomfort	1	-
Metallic taste	1	-
Nausea & abdominal discomfort	-	-
Nausea & heart burn	-	-
Nausea & metallic taste	-	-
Nausea & diarrhoea	-	-
Abdominal discomfort & heart burn	1	-
Pruitus / rashes	-	1
Pain at injection site	-	1
Total	6	2

This table shows the profile of side effects encountered.

The data shows that, 6 pregnant women out of 50 in group A had side effects, whereas only two pregnant women in group B had side effects.

This was statistically significant.

TABLE – VI

Birth Weight

Birth weight (kg)	Group A (Oral Iron)	Group B (Iron Sucrose)
< 2.5	5	None
2.5 -3	38	23

3 – 3.5	7	22
> 3.5	-	5
Total	50	50

This table shows a comparison of the baby weight at birth between the two groups. The data reveals that the birth weight in group B was comparatively higher than the birth weight in group A. Significant number of babies in group B, had birth weight above the average of Indian babies.

DISCUSSION

This study was conducted in PSG Institute of Medical Sciences & Research, during the period October 2008 to October 2009.

The study was conducted to compare the efficacy of iron sucrose with oral iron in the treatment of pregnant women with iron deficiency anemia.

The study was done to compare changes in hemoglobin values and serum ferritin levels, with oral iron and iron sucrose respectively.

The study was done to prove that iron sucrose is well-tolerated and more effective in restoring iron stores in pregnant women with anemia.

Total number of pregnant women included in the study were 100, between gestational age of 24 and 36 weeks, they were divided into two groups, group –A receiving 300mg of elemental iron daily and group – B, receiving iron sucrose therapy.

Rise in hemoglobin value and serum ferritin levels were checked, at entry into the study, after a period of 3 weeks and again after a period of 8 weeks, to note the improvement in the respective values. Majority of the pregnant women with hemoglobin values in the range of 6-9g/dl were in the gestational age of 28-32 weeks and hence had about 8 weeks time for the improvement in hemoglobin levels. Among the women who delivered before the second round of investigations could be repeated i.e. after 8 weeks, in these patients, the hemoglobin and serum ferritin values were measured just prior to delivery.

Finally at delivery, the birth weight of the baby was noted.

None of the 100 pregnant women in the study discontinued, making a total of 50 patients in group A and 50 patients in group B.

Patients in both the groups were administered folic acid along with the iron preparations.

Hemoglobin concentration :

The mean hemoglobin percentage of both groups was taken, and there was a significant increase in the iron sucrose group with a p-value <0.001, which was statistically significant.

Serum Ferritin values :

The mean serum ferritin value of both the groups was taken and there was a significant increase in the iron sucrose group with a p-value <0.001, which was statistically significant.

Birth weight :

We observed that in the iron sucrose group, women delivered babies with a higher birth weight, when compared with the oral iron group.

Side effects :

Only one patient in the iron sucrose group, with side-effects (pruritus), discontinued and was lost to follow-up.

Only one patient complained of pain at the injection site, in the iron sucrose group, but continued with the study.

The side effects in the oral group of patients was noted and corrective measures were taken, these patients continued with the study.

There was a notable increase in the hemoglobin and serum ferritin values at the end of the study, in the iron sucrose group.

Iron sucrose was found to restore iron stores faster and more effectively than oral iron.

CONCLUSION

Iron is needed in pregnancy, iron sucrose is an effective alternative to oral iron preparations.

The compliance of the pregnant women is higher with the iron sucrose therapy. Iron sucrose therapy is more effective in achieving the optimum results – an increase in hemoglobin concentration and an increase in ferritin levels.

Patients who were given iron sucrose had a better hemoglobin at delivery which will reduce maternal morbidity.

On an average, the birth weight was slightly higher in the iron sucrose group, when compared with the oral iron group.

Since iron sucrose has been proved to be well-tolerated, with minimal side effects, it is a suitable alternative to oral iron preparations in anemia complicating pregnancy.

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